REMARKS

Summary of Interview of July 3, 2003, and Telephone Conferences of July 8, 2003

Applicants thank Examiner Robinson for the courtesies extended during the interview on July 3, 2003. Although agreement was not reached on many topics, Examiner Robinson agreed to discuss the issues and points raised with Examiner Rotman, who was unfortunately not able to attend the interview.

Applicants' representative has received a copy of the Examiner's Interview Summary, which includes the subject matter of the telephone conferences. That Summary requires that this written reply to the last Office Action include the substance of the interview.

No exhibits were shown, and no demonstration was conducted. All claims were discussed. US 5,756,533, which is incorporated in the specification by reference, was discussed. No amendments were proposed or discussed.

Examiner Robinson agreed during the interview that it was appropriate to withdraw the finality of the outstanding office action. However, in the telephone conferences, Examiner Robinson indicated that the finality of the office action would not be withdrawn, even though the restriction requirement entered at Paper No. 9 is confusing and poorly phrased, it encompassed the elected species (the compound of Example 22). Applicants disagree that the restriction requirement, which requires "R^1=R^{20}=R^{21}", encompasses the elected species, at least because R^1 does not equal R^{20} or R^{21}.

Five main topics were discussed during the interview; the matters set forth in the Office Action dated January 14, 2003, were addressed *seriatim*. Specifically, Applicants pointed out that the group to which prosecution was restricted does not encompass the elected species. Applicants further traversed the restriction requirement as contrary to settled law and MPEP

guidance. Examiner Robinson confirmed that the rejection of claim 33 under 35 U.S.C. § 112, ¶1, had indeed been withdrawn, and the appearance thereof under "(old rejections)" was merely a typographical error.

Applicants also traversed the definiteness rejection of claims 34 and 37 and the rejection of all claims (19-37) as lacking enablement. Applicants also notified the Examiner that initialed copies of the forms PTO-1449 filed with the Information Disclosure Statement filed October 16, 2002, had not been received. Examiner Robinson found Applicants' copy in the PTO's file and provided it to Applicants.

The Office Action

The compound of Example 22 has been selected as the species to be examined, and claims 19-37 have been identified as reading on that compound and its uses.

All pending claims remain subject to a restriction requirement to a "natural genus." Claims 34 and 37 stand rejected under 35 U.S.C. § 112, first paragraph, as indefinite. Claims 19-37 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification is said not to provide enablement for R^3 (all heterocyclic rings) and R^4/R^5 (all nitrogen heterocyclic rings).

The restriction requirement and the rejections are addressed *seriatim* below.

1. **Election of Species and Restriction to a "Natural Genus"**

The restriction requirement is inconsistent with the chemical compound elected as the species to be prosecuted. As was discussed in the interview, Example 22, the elected species, requires, in pertinent part, that R^1 be methyl (alkyl) and that R^{20} and R^{21} be H (hydrogen). However, the restriction requirement that the examiner seeks to impose is recited as "$R^1=R^{20}=R^{21}$". Applicants pointed out that this is contrary to the requirements of the elected species, wherein R^1 does not equal R^{20} or R^{21}. Thus, as the restriction requirement is now

formulated, Applicants respectfully submit that the elected species is not a member of the "natural genus" to which the examiner seeks to restrict prosecution.

In the interview, Examiner Robinson also agreed that R^3 is recited in the requirement, even though it does not appear *in haec verba* as a pendant moiety in the structural formula set forth in claim 19, because the claim recites that R' represents radicals defined for R^3. Examiner Robinson also agreed that t=0, and not 1, in the compound of Example 22.

Applicants respectfully submit that the observation that "R^{20} and R^{21} can equal alkyl" in the second paragraph of the office action dated January 14, 2003, is not a reason for asserting that the compound of Example 22 fits within the "natural genus," as these substituents both are hydrogen in this elected species. Also, R^2 is defined as 'alkylthioaryl,' but Examiner Robinson agreed that this likely is merely a typographical error. R^2 cannot represent 'alkylthioaryl,' but it can represent arylthioalkyl. Examiner Robinson will confirm that this is merely a typographical error.

Further restriction of the claims to the "natural genus" proposed by the Examiner also was discussed. The Examiner has asserted that restriction of the claims to the "natural genus" proposed is appropriate because the genuses are independent and distinct inventions. One of the reasons set forth in support of this assertion is that some parts of the claim may be patentable over art that precludes patentability of other parts of the claim. Applicants respectfully submit the further restriction requirement is improper not only because the claims contain but a single inventive concept, but also because the proposed "natural genus" is contrary to settled judicial precedent and MPEP guidance. In particular, this approach is contrary to MPEP § 803.02.

It is important to note that the restriction requirement in question is a *further* requirement. Applicants first were required to elect a species, and identified claims 19-37 as reading thereon.

The Examiner then made this further requirement based on "a liberal interpretation of the doctrine of legal and chemical equivalence." Thus, the recitations in the office action notwithstanding, this further requirement is based on matters *other than* the only properly used bases for restriction, i.e., that the inventions are independent and distinct. Rather, the restriction requirement is based on the variety of moieties pendant from the core of the compound claimed. However, "legal and chemical equivalence" is not a basis for requiring restriction.

Applicants respectfully traverse these reasons and the further requirement of restriction to the "natural genus" arbitrarily defined in the Office Action. In response to the statements in the Office Action, Applicants respectfully submit that the inventive concept of claims 19-37 is but a single inventive concept (i.e., there is unity of invention), and the use of 'legal and chemical equivalence' to further require restriction is not founded in law. The compounds of claim 19 are retroviral protease inhibitors. The compounds of claim 19 have a single core and pendant moieties, as set forth in the definitions of the substituents. No matter which combination of pendant moieties is selected, the resulting compound is a retroviral protease inhibitor. Such compounds may also have other uses, but all are retroviral protease inhibitors.

To further restrict the pending claims to any scope less than their full scope under a doctrine based on 'legal and chemical equivalence' is contrary to established precedent and MPEP guidance. This further restriction to a "natural genus" is not based on the independence and distinctness of the 'inventions.' Rather, Applicants respectfully submit that this further restriction is equivalent to asserting that the Markush groups are improper. Indeed, Applicants respectfully submit that the inventions cannot be independent and distinct if the inventions are 'legally and chemically equivalent.'

The "natural genus" is not based in independence and distinctness of the 'inventions.' The Examiner has not articulated a distinction between the 'inventions' that is based on 'legal equivalence,' and has not described how this 'legal equivalence' operates to make the 'inventions' independent and distinct. Indeed, Applicants respectfully submit that this phrase is meaningless. The Examiner has not articulated a distinction between the 'inventions' that is based on 'chemical equivalence,' and has not described how this 'chemical equivalence' operates to make the 'inventions' independent and distinct. Applicants respectfully submit that the Examiner cannot do so because, to the extent this phrase has any meaning, all of the claimed compounds are retroviral protease inhibitors.

This approach, i.e., the splitting of Markush groups such as are set forth in the pending claims, has been rejected by the Courts and by the United States Patent and Trademark Office. The proposed restriction would have split the claims into only two groups, the 'natural genus' and everything else. Thus, the additional burden of examining the remainder of the claim would not be great. As set forth in MPEP § 803.02,

> If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they are directed to independent and distinct inventions.

This same section of the MPEP further states:

> it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention.

The MPEP cites *In re Harnisch* and *Ex parte Hozumi*, 3 U.S.P.Q.2d 1059, for this proposition.

In *In re Harnisch*, 206 U.S.P.Q. 300 (C.C.P.A. 1980), the C.C.P.A. precluded use of such rejections when there is unity of invention in the claim. In *Harnisch*, the Board rejected a

compound claim reciting Markush groups as drawn to improper Markush groups. *Id.* at 301. The members of the groups were said not to belong to a recognized genus and to possess divers physical or chemical properties. The compounds were said not to be functionally equivalent and so dissimilar as to preclude associating them in a generic group. The functional equivalence of the compounds was said not to be recognized in the art.

The assertions of the Board in *Harnisch* relating to functional equivalence that were rejected by the *Harnisch* court are the same arguments set forth in support of the further restriction at issue here. However, the Court rejected these lines of argument because all of the compounds had a single use, and thus had unity of invention.

Harnisch notes that this unity of invention concept is not to be confused with restriction practice under 35 U.S.C. § 121. *Id.* at 305. Indeed, this is the point that Applicants assert here; that the concept of 'legal and chemical equivalence' is *not* to be used in support of a restriction requirement couched in terms of 35 U.S.C. § 121, as the Examiner has done here. Also, "it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention." MPEP § 803.02. Herein, the claim clearly does not lack unity of invention.

The Office Action includes the assertion that compounds of the invention formed from various pendant moieties recited in the Markush groups form a separate genus because they have separate status in the art. At the interview, the Examiner emphasized the uses of the compounds, apparently because different moieties may provide compounds having different uses, and the differences in their chemical structures.

Applicants respectfully submit that claimed compounds may have different uses other than the utility described in the specification is not a sound reason for requiring restriction.

Rather, this argument is like that set forth in *In re Jones*, 162 F.2d 479, 74 U.S.P.Q. 149 (C.C.P.A.1947). In *Jones*, the Board had rejected a claim containing a Markush group and directed to compounds that were plant growth stimulators because the compounds also were plant growth regulators, fungicides, and insecticides. The Court reversed this 'improper Markush group' rejection because the claimed compounds had a common function. As in *Jones*, the Examiner's concerns here about potentially different uses for these compounds are not legally cognizable, as they all have the same use as retroviral protease inhibitors.

Similarly, the Examiner's concerns about the differences in the chemical structures of the claimed compounds are not legally cognizable. The Commissioner settled this matter in *Ex parte Clark*, 11 U.S.P.Q. 52 (Comm. Pats. 1931), which permitted inclusion in a Markush group of aliphatic, aromatic, and aralkyl compounds. Applicants' representatives also identified *Ex parte Dahlen*, 42 U.S.P.Q. 208 (Bd. App. 1938), wherein the Board permitted claims to compounds having a common core and side chains having wide variations because the claimed compounds had a community of properties. Herein, the claimed compounds have a common core and side chains (although the Examiner disputed that the compounds have such a core/side chains construction) and have the same property as retroviral protease inhibitors. Similarly, rejection of a claim for a Markush group that the Board agreed was broad was not upheld in *Ex parte Hozumi*, 3 U.S.P.Q.2d 1059 (Bd. Pat. App. & Interf. 1984) because of the significant areas of commonality of the claimed compounds. As in this application, the *Hozumi* compounds were core structures having plural diverse pendant moieties.

MPEP § 803.02 establishes a procedure for examination of such claims. Indeed, the MPEP recites that a Markush-type claim can include independent and distinct inventions "where two or more of the members are so unrelated and diverse that a prior art reference anticipating

the claim with respect to one of the members would not render the claim obvious under 35 U.S.C. 103 with respect to the other member(s)." This one of the bases the Examiner has relied upon for restriction. However, the guidance of the MPEP is to continue examination of the entirety of the claim.

> In applications containing claims of that nature, the examiner may require a provisional election of a single species prior to examination on the merits. The provisional election will be given effect in the event that the Markush-type claim should be found not allowable. Following election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability. If the Markush-type claim is not allowable over the prior art, examination will be limited to the Markush-type claim and claims to the elected species, with claims drawn to species patentably distinct from the elected species held withdrawn from further consideration.
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> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a *non-elected species*, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration.

Applicants respectfully submit that claims 19-37 are directed to a single inventive concept, i.e., retroviral protease inhibitors and their uses. The proposed "natural genus" is neither natural nor a genus, and is not based on sound legal principles. The concept of "legal and chemical equivalence" on which the proposed restriction is based is not sound support for the assertion that the 'inventions' in the claims are independent and distinct. Rather, it is in reality a concept that was rejected long ago by the Commissioner and the Courts, and continues to be rejected.

Applicants respectfully submit that the approach taken is contrary to the principles of examination established in the MPEP. After the species was elected, the remainder of the claim

should have been examined on the merits in accordance with MPEP § 803.02. The Examiner's claims of burden on the Patent Office ring hollow in view of the fact that the claim was split into only two parts. The single inventive concept of claims 19-37 should be examined in their entireties.

2. **The Rejection of Claim 33 under 35 U.S.C. § 112, ¶ 1**

Examiner Robinson agreed that there appeared to be a typographical error in the Office Action relating to this utility rejection. Whereas the Office Action states that the rejection had been withdrawn in view of Applicants' argument in paper 8B, the rejection again appeared under a section marked "(old rejections)."

Examiner Robinson agreed that the appearance of the rejection under 'old rejections' appeared to be a typographical error. However, Examiner Robinson indicated an intent to withdraw the finality of the rejection to re-assert this rejection; the basis for the re-assertion was not made clear during the interview. Now that the finality of the rejection has not been withdrawn, this rejection must be considered withdrawn.

3. **The Rejection of Claims 34 and 37 under 35 U.S.C. § 112, ¶ 2**

Claims 34 and 37 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as their invention. The Office Action contends that (1) the phrases "a retroviral infection" (claim 34) and "in combination with other drugs" (claim 37) are indefinite because no particular retroviral infection or other drug is being claimed. Applicants respectfully traverse this rejection.

Regarding claim 34, retroviral infections are well known and have a definite meaning to the ordinary skilled artisan. As stated above, retroviral infections arise from HIV and other

lentiviruses such as HIV-2, respiratory syncitial virus, hepadnavirus, picornavirus, and cytomegalovirus. Not only are retroviral infections well known, the above retroviruses and others are disclosed in U.S. Patent No. 5,756,533, incorporated into the application by reference. The '533 patent also discloses the treatment of retroviral infections by inhibiting retroviral protease.

Because the meaning of "a retroviral infection" is well known in the art and is also clear from the specification, Applicants submit that claim 34 is not made indefinite simply because no specific retrovirus, or disease (*e.g.*, AIDS) resulting from a retroviral infection, is recited. The Office Action's contention that Applicants have "not shown how all of these various retroviral infections or even most of them can be treated" by the claimed compounds has absolutely no bearing on the issue of whether the term "a retroviral infection" is definite within the meaning of 35 U.S.C. § 112, second paragraph.

Regarding claim 37, the phrase in question is not simply "in combination with other drugs." Rather, the phrase is "in combination with other drugs for the treatment of AIDS or the symptoms of AIDS." Applicants respectfully submit that the meaning of "drugs for the treatment of AIDS or the symptoms of AIDS" is not only known in the art but is also set forth in the specification at page 167, line 10 to page 168, line 10. In contrast to what the Office Action contends, the term is not rendered indefinite merely because it encompasses "a vast array of drugs with varying structures." It is well established that breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 U.S.P.Q. 597 (C.C.P.A. 1971) and MPEP 2173.04.

During the interview, it was suggested that the rejection would stand simply because the chemical formulas of these other drugs were not disclosed and claimed. Applicants respectfully submit that it is unnecessary to specifically identify the chemical formulas of these drugs.

For these reasons, Applicants submit that claims 34 and 37 are definite and respectfully request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

4. The Rejection of Claims 19-37 under 35 U.S.C. § 112, ¶ 1

Claims 19-37 stand rejected under 35 U.S.C. § 112, first paragraph for lacking sufficient enablement for the making and using compounds within the claimed scope. The rejection is based on assertions that selected R^3/R' (all heterocycles) and R^4/R^5 (selected N-containing heterocyclic rings) are not enabled. Applicants respectfully traverse this rejection.

It is well established that Applicants are entitled to a presumption of enablement. *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995). Specifically,

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. (emphasis added).
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> *In re Marzocchi and Horton*, 169 USPQ 367, 370 (C.C.P.A. 1971).

The Office Action fails to provide a single technical reason or a hint of objective evidence to rebut the presumption of enablement relating to use of the claimed invention. Instead, the Office Action observes that "only one compound falling within the elected restriction group were [sic] only tested for enzyme inhibition, antiviral activity, and cell toxicity, where the R^3 is methyl, and the R^4 and R^5 come together to form saturated isoquinoline. [*sic*]" The Office Action offers this one observation as allegedly bearing on the 5th, 6th, and 7th of the so-called *Wands* factors.

Note that the saturated isoquinoline (R^4/R^5 structure) exemplified and tested is a nitrogen-containing heterocyclic ring. In any event, the number of compounds tested has absolutely no bearing on the 5th *Wands* factor, which is the level of predictability *in the art.* Third, the Examiner's contention that "[t]he applicant does not test the whole breadth of compounds encompassing all of the moieties that these particular radicals can be" is totally irrelevant. It is manifest that no working examples are required to satisfy enablement, let alone examples directed to every claimed radical group. *In re Fouche*, 169 USPQ 429, 434 (C.C.P.A. 1971). In any event, the high chemical and biological activity and low toxicity of the compounds tested according to the enzyme and CEM cell assays are as described and reported at 154, line 14 to page 161, line 3.

Nor does the Office Action cite any objective evidence showing that even a single claimed compound would not possess inhibitory activity. The Office Action states summarily that the *Wands* factor on undue experimentation is satisfied merely because multiple radical groups are claimed. During the interview, Examiner Robinson suggested a lack of enablement could be found because potency may be affected when these radicals are interchanged. The key to a rejection based on lack of enablement is whether *undue* experimentation is required. In the claimed invention, the compounds inhibit retroviral protease. Undue experimentation is not required to identify an inhibitory compound. Because the compounds necessarily do not have identical potency (*Fouche*, 169 U.S.P.Q. at 434), it likely will be necessary to adjust dosage. However, such dosage adjustments are not considered *undue* experimentation. *US v. Telectronics*, 8 U.S.P.Q. 2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). Rather, dose/response studies are within the skill of a practitioner, and do not constitute undue experimentation. *Telectronics*, 8 U.S.P.Q. 2d at 1224.

The Office Action fails to rebut the presumption of enablement of a skilled practitioner's ability to make the claimed invention. The Office Action provides neither rationale why nor evidence that a person skilled in the art would have doubted that any of the claimed compounds could have been routinely made according to procedures detailed in the specification, or that any such compound would possesses the asserted utility as a retroviral protease inhibitor. Indeed, numerous methods of making the compounds are described at page 25, line 4 to page 154, line 12, of the specification. Methods of using the invention are described at page 161, line 8 to page 168, line 9.

Nothing in the record suggests that undue experimentation would have been required to (i) synthesize compounds within the claims, and (ii) test the compounds for protease inhibition activity as described in the specification with a reasonable expectation that the tested compound would exhibit some degree of the asserted activity.

In summary, Applicants respectfully submit that the Examiner's subjective feeling about the number of examples is not a well-founded legal position. Rather, the Office Action improperly tries to shift the burden to Applicants to demonstrate that the claims are enabled, without first providing the legally required, objective evidence to question the asserted enablement of the claimed compounds. The rejection therefore completely ignores the presumption of enablement to which Applicants are entitled. *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995).

In any event, Applicants respectfully submit that the points raised herein illustrate that the claims are enabled and the rejection is traversed. For all of the above reasons, Applicants submit that claims 19-37 are enabled by the specification and respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

5. **Inf rmation Disclosure Statement**

Applicants had not received initialed Forms PTO-1449 relating to the Information Disclosure Statement filed October 16, 2002. When Applicants' representatives mentioned this at the interview, Examiner Robinson provided a copy that had mistakenly been filed in the PTO's file. Review of the forms PTO-1449 attached thereto indicated that a number of documents had not been considered. Examiner Robinson indicated that she did not receive those items. Therefore, Applicants have again submitted those documents together with an Information Disclosure Statement and forms PTO-1449. These documents provide skilled practitioners information in support of Applicants' positions regarding enablement and definiteness beyond that found in the specification of this application.

Further Considerations

In further support of Applicants' remarks, Applicants' representatives noted that the proposed further restriction requirement and the rejections of the claims set forth in the Office Action ignore the knowledge in the art. In particular, issued patents contain only part of the information available to skilled practitioners. For example, Applicants again note that US 5,765,533, which is incorporated by reference in the subject application, identifies types of retroviral infections treatable in accordance with the claimed invention. This citation thus answers the question set forth in the last Office Action: "Which retroviral infection is the applicant claiming?"

These issued patents also illustrate that descriptions of the style found herein routinely are found sufficient to support grant of claims of the style found herein. When this point was raised, Examiner Robinson's response was that each patent is individual, is examined on its own merits, is *only presumed* to be valid and may be invalid, and should not be used to guide

examination of this application. Applicants respectfully submit that such patents are *at least* indicia of the skill in the art with respect to the indefiniteness and enablement rejections. These patents *at least* identify "other drugs for the treatment of AIDS or the symptoms of AIDS," as recited in claim 37, and identify what those symptoms are. These patents *at least* identify retroviral infections that can be treated, as recited in claim 34.

On the point of examination of this application specifically, Applicants direct the Examiner's attention to US 6,538,006. The application from which this patent issued (09/743,460) was identified in the Information Disclosure filed October 16, 2002. The '006 patent is related to provisional application No. 60/092,090, as is the present application. Indeed, it is believed that the specification of the '006 patent is identical to the specification of the present application. The claims of the '006 patent are directed to compounds of "Formula III" in the applications.

Comparison of the claims of the '006 patent with the claims pending herein is instructive. As can be seen, the compound claims of each document are in the form of a core with pendant moieties. The Markush-type definitions of pendant moieties R^1, R^2, R^3, R^4/R^5, R^6, and Y' in the '006 patent are identical to those which the Examiner proposes to restrict herein. The corresponding claims directed to a method of inhibiting a retroviral infection (claim 34 herein) and a method of treating AIDS comprising administering a pharmaceutical composition of the invention together with other drugs for the treatment of AIDS or the symptoms of AIDS (claim 37) also are identical.

Applicants respectfully submit that the '006 is evidence that the proposed "natural genus" is not well-founded; that claims 34 and 37 are definite; and that the claims are enabled, as the method of making and using the invention is sufficiently described in the specification.

CONCLUSION

Accordingly, for all of the above reasons, all pending claims of this application are believed to be in condition for allowance, and such action is respectfully requested. This response is believed to completely address all of the substantive issues raised in the Final Office Action dated January 14, 2003.

Respectfully submitted,

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